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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/365, 31/19, 31/215, 7/06

A1

(11) International Publication Number: WO 96/20703

(43) International Publication Date: 11 July 1996 (11.07.96)

(21) International Application Number: PCT/AU96/00003

(22) International Filing Date: 5 January 1996 (05.01.96)

(30) Priority Data:

PN 0420	6 January 1995 (06.01.95)	AU
PN 6777	24 November 1995 (24.11.95)	AU
PN 6977	5 December 1995 (05.12.95)	AU

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(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

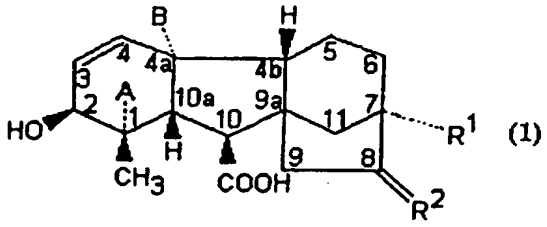
Published

With international search report.
With amended claims.

(54) Title: COMPOUNDS FOR VETERINARY AND MEDICINAL APPLICATIONS

(57) Abstract

Compounds of formula (1) (Gibberellins), and their pharmaceutically acceptable derivatives when used as promoters of lesion-healing, ulcer-healing, wound-healing or cultivation of skin cell lines or hair growth on animals, including humans, wherein A is COOR, where R is hydrogen, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, amidine, NR^4R^5 or an unsaturated or saturated ring containing one or more hetero-atoms. R^4 and R^5 may or may not be the same, are hydrogen, or C_{1-20} alkyl, allyl, aryl, aralykyl or an unsaturated or saturated ring containing one or more hetero-atoms; B is hydrogen, hydroxyl, mercaptan, halogen; or A and B together form a -CO-O- linkage; R^1 is hydrogen, hydroxyl, mercaptan, halogen, amino, azido, NR^4R^5, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl; and R^2 is methylene, hetero-atoms.



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Compounds For Veterinary and Medicinal Applications

This invention relates to a novel application of Gibberellins in veterinary and human medicines. In particular the invention concerns Gibberellins' pharmaceutical formulations and their use as ulcer-healing and wound-healing promoters, and their related applications.

Gibberellins are a series of naturally occurring compounds which are known as plant growth regulators that are widely spread in the plant-kingdom.[1] They have also been isolated from metabolites of some micro-organisms, such as Gibberella fuzikuroi.[2] Gibberellins, especially Gibberellic Acid (Gibberellin A_3), have been used extensively in agriculture to increase the growth of some fruits (strawberries and grapes) and vegetables (tomatoes, cabbages and cauliflowers), also as food additive in the malting of barley.[3] However, to date, no application in veterinary and human medicines has been reported.

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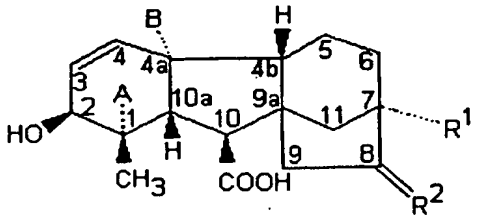
We have now found that Gibberellins, especially, Gibberellic acid (Gibberellin A_3) and/or mixture of Gibberellin A_3 and A_7 are promoters of ulcer-healing, wound-healing and cultivation of skin cell lines, which would play a

significant role in veterinary and human medicines. This invention therefore provides a series of novel applications of compounds of formula (1) in both veterinary and human medicines,



(1)

wherein A is COOR, where R is hydrogen, unsubstituted or substituted (e.g. halogenated) C_{1-20} alkyl, (e.g. methyl, ethyl), allyl, aryl, (e.g. phenyl), arylalkyl, amidine, NR^4R^5 or an unsaturated or saturated ring containing one or more hetero-atoms (e.g. nitrogen, oxygen or sulphur). R^4 and R^5 which may or may not be the same, are hydrogen, or C_{1-20} alkyl (e.g. methyl, ethyl), allyl, aryl, aralykyl or an unsaturated or saturated ring containing one or more hetero-atoms (e.g. nitrogen, oxygen, sulphur),

B is hydrogen, hydroxyl, mercaptan, halogen (e.g. Cl, F),

or A and B together form a -CO-O- linkage,

R^1 is hydrogen, hydroxyl, mercaptan, halogen, (e.g. F, Cl), amino, azido, NR^4R^5, unsubstituted or substituted (e.g. halogenated) C_{1-20} alkyl, allyl, aryl, arylalkyl, and

R^2 is methylene, hetero-atoms (e.g. oxygen, sulphur).

In the case of Gibberellin A_3, A-B is —— CO-O ——, R^1 is hydroxyl, R^2 is methylene.

Pharmaceutically acceptable salts of the compounds of formula (1) include alkali metal (e.g. sodium, potassium), alkaline earth metal (e.g. calcium, magnesium), ammonium, and organic bases such as $NR^6R^7R^8R^9$ (where R^6, R^7, R^8, R^9 which may be the same or not the same, are C_{1-20} alkyl or alkanol, aryl), procaine, lidocaine etc..

Pharmaceutically acceptable combination of the compounds of formula (1) may also be formed by combining them with one or more other active ingredients, for example, urea, antibiotics (e.g. streptomycin, getamycin, kanamycin, neomycin, penicillin, cephalosporin, rifamycin), antiseptic agents (e.g. cetylpyridinium chloride, benzoic acid salt), Vitamins (e.g. Vitamin E), sucrose, b-1,3-glucan, surfacants, cream-bases, other herbs (e.g. panax pseudoginseng).

References hereinafter to the compounds of formula (1) include the compounds of formula (1), and their pharmaceutically acceptable derivatives thereof.

The compounds of formula (1) possess activities of promoting ulcer-healing, wound-healing and cultivation of skin cell lines, possibly by stimulating cell division, hastening circulation and promoting repairing. There is thus provided in a further aspect of the invention the compounds of formula (1) for use as an active therapeutic agent, in particular as an ulcer-healing and wound-healing agent in the treatment of lesions, ulcers, wounds and related conditions, for example, in the treatment of surface-wounds, surgical wounds, open fractures, bronchitis, dermatitis, thrombophlebitis, leg ulcer, peptic ulcer, aphthous ulcer, decubitus. There is also provided in a further aspect of the invention the compounds of formula (1) for use as an active agent in promoting the cultivation of skin cell lines for plastic surgery.

In a further or alternative aspect there is provided a method for the treatment of lesions, ulcers, wounds and related conditions in mammals including humans comprising administering of an effective amount of the compounds of formula (1).

There is also provided in a further or alternative aspect use of the compounds of formula (1) of the manufacture of a medicament for the treatment of lesions, or wounds or ulcers, or related conditions.

The amount of the compounds of formula (1) required for use in treatment will vary with the route of administration, the nature of the condition being treated and the age, condition and type of the animal patient, (including human patients), and will ultimately be at the discretion of the attendant veterinarian or surgeon.

In general a suitable dose will be in the range of from about 0.1μg to 50mg/kg of body weight per day, preferably in the range of 0.1μg to 2,000μg/kg/day. Treatment is preferably commenced after or at the time of ulcer or wound occurs and continues until ulcer or wound is healed. Suitably treatment is given 1~4 times daily and continued for 3~30 days. Alternatively, in some cases like open fracture or internal surgical wounds, a single treatment may be administered on the spot.

The desired dose may be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

The compounds of formula (1) are conveniently administered in unit dosage form for example containing 0.1 to 50mg of active ingredient per unit dosage form.

While it is possible that, for use in therapy, the compounds of formula (1) may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation including the compounds of formula (1) or a pharmaceutically acceptable derivative thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, intradermal, sub-cutaneous and intravenous) administration or in a form suitable for administration to the gastrointestinal tract, or in a form suitable for administration to the respiratory tract (including the nasal passages) for example by inhalation or insufflation or for intradermal or sub-cutaneous implantation or for transdermal patch. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical formulations suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution, a suspension or as an emulsion. The active ingredient may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of,

for example, aqueous of oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The compounds of formula (1) may also be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

For topical administration to the epidermis the compounds of formula (1) may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening, or colouring agents.

For topical administration in the mouth, the compounds of formula (1) may be formulated as lozenges comprising active ingredient in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

For vaginal administration the formulations may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

For rectal administration, unit dose suppositories wherein the carrier is a solid are preferred. Suitable carriers include cocoa butter and other materials commonly

used in the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in moulds.

For administration to the respiratory tract (including intranasal administration) compounds of formula (1) may be administered by any of the methods and formulations employed in the art for administration to the respiratory tract.

Thus in general the compounds of formula (1) may be administered in the form of a solution or a suspension or as a dry powder.

Solutions and suspensions will preferably be aqueous for example prepared from water alone (for example sterile or pyrogen-free water) or water and a physiologically acceptable co-solvent (for example ethanol, propylene glycol, polyethylene glycols such as PEG 400).

Such solutions or suspensions may additionally contain other excipients for example preservatives (such as benzalkonium chloride), solubilising agents/surfactants such as polysorbates (e.g. Tween 80, Span 80, benzalkonium chloride), buffers, isotonicity-adjusting agents (for example sodium chloride), absorption enhancers and viscosity enhancers. Suspensions may additionally contain suspending agents (for example microcrystalline cellulose, carboxymethyl cellulose sodium).

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case a means of dose metering is desirably provided. In the case of a dropper or pipette this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray this may be achieved for example by means of a metering atomizing spray pump.

An aerosol formulation may also be used for the respiratory tract administration, in which the compounds of formula (1) are provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane or dichlorotetrafluoroethane, carbon dioxide or other suitable gas. The aerosol may conveniently also contain a

surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the compounds of formula (1) may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidine (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of e.g. gelatin or blister packs from which the powder may be administered by means of an inhaler.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronisation.

For administration to the gastrointestinal ulcer such as peptic ulcer, the compounds of formula (1) or a pharmaceutically acceptable derivative may be administered by any of the methods and formulations employed in the art for administration to the gastrointestinal tract.

When desired, formulations adapted to give sustained release of the active ingredient may be employed.

The compounds of formula (1) may also be used in combination with other therapeutic agents, for example other anti-infective agents, such as antibiotics or wound healing agents such as 1,3-β-glucan. The invention thus provides in a further aspect a combination comprising the compounds of formula (1) or a pharmaceutically acceptable derivative thereof together with another therapeutically active agent.

The combinations mentioned above may conveniently be presented for use in the form of a pharmaceutical formulation and thus such formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier therefore comprise a further aspect of the invention.

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When the compounds of formula (1) are used with a second therapeutic agent active in wound-healing, the dose of each compound may either be the same as or differ from that employed when each compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

The compounds of formula (1) and their pharmaceutically acceptable derivatives may be prepared by any methods known in the art for the preparation of compounds of analogous structure.

In addition to the findings described above, we have also discovered that the compounds of formula (1) promote hair growth in mammals including human. This is a logical extension of what is believed to be their mode of action which involves stimulating cell division. This provides another aspect of this invention wherein the compounds of formula (1) and their pharmaceutically acceptable derivatives may have potential commercial applications, such as acting as an active ingredient for human hair care product or promoting wool production in the sheep-farming industry.

The present invention is further described by the following drawings and examples which are for illustrative purposes only and should not be construed as a limitation of the invention.

Drawings:

Figure 1 shows the ^{1}H-nmr spectrum for the free acids of compounds of Formula 1.

Figure 2 shows the IR spectrum for the free acids of compounds of Formula 1.

Figure 3 shows the ^{1}H-nmr spectrum for the sodium salts of compounds of Formula 1.

Figure 4 shows the IR spectrum for the sodium salts of compounds of Formula 1.

Methods:

Material: The compounds of formula (1) used in the following experiments were free acid (its ^{1}H-nmr showed in figure 1, and IR spectrum showed in figure 2) and/or sodium salt (its ^{1}H-nmr showed in figure 3, and IR spectrum showed in figure 4).

Statistical analysis: All statistical analysis for the following experimental results were performed two-tailed at a significance level of P=0.05.

Example 1. Topical use of compounds of formula (1)

The compounds of formula (1) may be used topically as their aqueous solution or in oil base as ointment form at a concentration of 0.1 to 20,000μg per milli-litre, preferably at 0.1 to 100μg/ml.

Example 2. Surface-wound healing

Gibberellin A_3 (1mg) was dissolved in ethanol (1ml), then diluted with distilled water (99ml) to make a solution at a concentration of 10μg/ml. This solution was directly applied on wounds (cuts, at about 2cm in length, and about 1mm in depth) of pigs by spreading the solution twice a day until the wounds healed. The control group of the animals was treated with 1% ethanol aqueous solution. The average rates of wound healing increased by one third in Gibberellin-administered group compared to the controls in this double-blind experiment.

Example 3. Surface-wound healing

Gibberellin A_3 sodium salt was used in aqueous solution (20μg/ml) instead of Gibberellin A_3 free acid mentioned in example 2. The similar results as example 2 were obtained.

Example 4. Surface-wound healing

A solution containing 10μg/ml Gibberellin A_3 sodium salt and 500μg/ml urea was used. The similar animal experiment mentioned in example 2 was conducted. About 25% of increase of wound healing rates in Gibberellin A_3 and urea administered group compared to the control group using only urea solution was observed in this double-blind experiment.

Example 5. Chronic ulceration of leg caused by varicose vein

Gibberellin A_3 or a mixture of A_3 and A_7 (2mg) was dissolved in ethanol (1ml), then diluted with distilled water (99ml). This resulting solution was spread on the

surface of the ulcer twice a day for a period of five days to three weeks. An 85% efficacy was observed.

Example 6. Some Double-blind trials for Gibberellin A_3 sodium salt

Case of treatment	Administration			Efficacy
	Route	Dosage or concentration	Duration	
Thrombophlebitis	topical	20~50μg/ml, 2~4 times daily	5 days to 4 weeks	85%
Open fracture	topical on the spot of wound	200~500μg/ml*1, once only		75% (increased recovery rate by 10%)
Bronchitis	aerosol for respiratory tract	5~10μg/ml*2, 2~4 times daily	3 days to 2 weeks	80%
Dermatitis	topical	10~20μg/ml, 2~4 times daily	5 days to 3 weeks	65%
Peptic ulcer	oral	5mg*3, twice daily	2 to 4 weeks	85%
Aphthous ulcer	topical (gargle)	50~1000μg/ml*4, 2~3 times daily	3 days to 2 weeks	80%
Decubitus	topical	20~50μg/ml*5, 2~4 times daily	5 days to 3 weeks	75%
Hair-growth promotion	topical	20~50μg/ml, once a day	2 weeks to 4 months	70%

*1. Combination with antibiotics such as neomycin sulfate.

*2. In some cases patients were also treated with antibiotics such as amoxicillin.

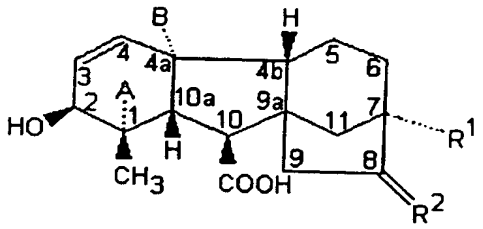
*3. Combination with antibiotics such as streptomycin sulfate (0.5g)/ampicillin (0.5g), and bismuth citrate, or milk-starch, and/or ranitidine.

*4. In some cases, combination with cetylpyridinium chloride as anticeptic agent.

*5. Combination with antibiotics such as Midecamycin/Doxycycline.

CLAIMS:

1. Compounds of formula (1), (Gibberellins), and their pharmaceutically acceptable derivatives when used as promoters of lesion-healing, ulcer-healing, wound-healing or cultivation of skin cell lines or hair growth on animals, including humans,



(1)

Wherein A is COOR, where R is hydrogen, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, amidine, NR^4R^5 or an unsaturated or saturated ring containing one or more hetero-atoms. R^4 and R^5 may or may not be the same, are hydrogen, or C_{1-20} alkyl, allyl, aryl, arylalkyl or an unsaturated or saturated ring containing one or more hetero-atoms,
B is hydrogen, hydroxyl, mercaptan, halogen,
or A and B together form a -CO-O- linkage,
R^1 is hydrogen, hydroxyl, mercaptan, halogen, amino, azido, NR^4R^5, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, and
R^2 is methylene, hetero-atoms.

2. Compounds of claim 1, wherein the Gibberellins are Gibberellin A_3 so that A-B is -CO-O-, R^1 is hydroxyl and R^2 is methylene.

3. Compounds of claim 1, wherein the Gibberellins are a mixture of Gibberellin A_3 and Gibberellin A_7.

4. Compounds of claim 1 wherein the pharmaceutically acceptable derivatives are salts, including alkali metal salts, alkaline earth metal salts, and salts of ammonium, organic bases such as $NR^6R^7R^8R^9$ (where R^6, R^7, R^8, R^9 which may be the same or not the same, are C_{1-20} alkyl or alkanol, aryl), procaine, or lidocaine.

5. The compounds of any one of claims 1 to 4, when used as active therapeutic agents in the treatment of lesions, ulcers, and surface-wounds, surgical wounds,

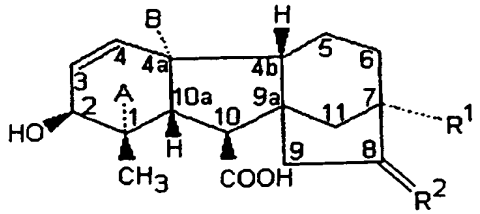
open fractures, bronchitis, dermatitis or thrombophlebitis on a patient in need thereof.

6. The compounds of any one of claimes 1 to 4, when used as active therapeutic in the treatment of leg ulcer, peptic ulcer, aphthous ulcer, decubitus.

7. The compounds of any one of claims 1 to 4 when used as active agents in the promotion of cultivation of skin cell lines for plastic surgery.

8. The compounds of any one of claims 1 to 4 when used as promoters of hair-growth, in stimulation of wool production or as an active ingredient in human hair care products.

9. A pharmaceutical composition including a compound of formula (1)



(1)

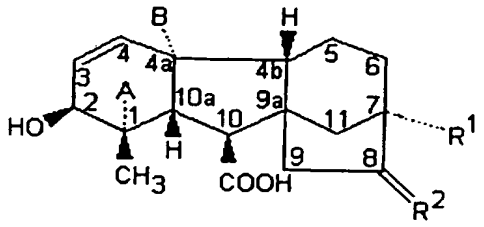
wherein A is COOR, where R is hydrogen, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, amidine, NR^4R^5 or an unsaturated or saturated ring containing one or more hetero-atoms. R^4 and R^5 may or may not be the same, are hydrogen, or C_{1-20} alkyl, allyl, aryl, arylalkyl or an unsaturated or saturated ring containing one or more hetero-atoms,
B is hydrogen, hydroxyl, mercaptan, halogen,
or A and B together form a -CO-O- linkage,
R^1 is hydrogen, hydroxyl, mercaptan, halogen, amino, azido, NR^4R^5, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, and
R^2 is methylene, hetero-atoms and a pharmaceutically acceptable carrier.

10. A pharmaceutical composition according to claim 9 wherein the carrier is selected from sucrose, acacia, tragicanth, gelatin, glycerin, cocoa butter, propylene glycol, polyethylene glycols, benzolkamium chloride, polysorbates, buffers, isotonicity-adjusting agent, absorption enhancers, viscosity enhancers, suspending agents, sufactants, lactose, starch or starch derivatives and mixtures thereof.

11. A pharmaceutical composition according to claim 9 or claim 10 containing one or more active ingredients in addition to compounds of formula (1).

12. A pharmaceutical composition according to claim 11, wherein the additional active ingredient is selected from urea, antibiotics, antiseptic agents, vitamins, β-1,3-glucan, medicina herbs or mixtures thereof.

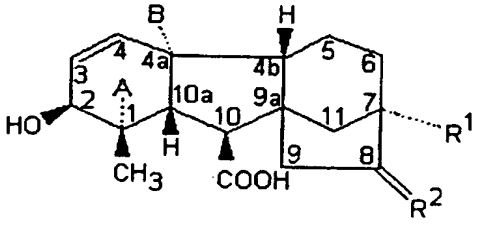
13. A method of promoting ulcer-healing or wound-healing or promoting hair growth including administering an effective amount of a compound of formula (1)



(1)

wherein A is COOR, where R is hydrogen, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, amidine, NR^4R^5 or an unsaturated or saturated ring containing one or more hetero-atoms. R^4 and R^5 may or may not be the same, are hydrogen, or C_{1-20} alkyl, allyl, aryl, arylalkyl or an unsaturated or saturated ring containing one or more hetero-atoms,
B is hydrogen, hydroxyl, mercaptan, halogen,
or A and B together form a -CO-O- linkage,
R^1 is hydrogen, hydroxyl, mercaptan, halogen, amino, azido, NR^4R^5, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, and
R^2 is methylene, hetero-atoms to a patient in need thereof.

14. A method of promoting growth of skin cell lines including providing an effective amount of a compound of formula (1)



(1)

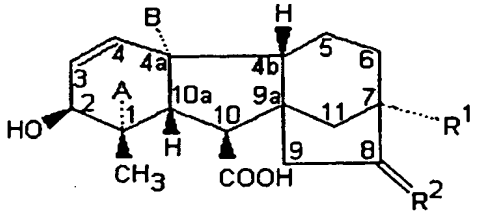
wherein A is COOR, where R is hydrogen, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, amidine, NR^4R^5 or an unsaturated or saturated ring containing one or more hetero-atoms. R^4 and R^5 may or may not be the same, are hydrogen,

or C_{1-20} alkyl, allyl, aryl, arylalkyl or an unsaturated or saturated ring containing one or more hetero-atoms,
B is hydrogen, hydroxyl, mercaptan, halogen,
or A and B together form a -CO-O- linkage,
R^1 is hydrogen, hydroxyl, mercaptan, halogen, amino, azido, NR^4R^5, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, and
R^2 is methylene, hetero-atoms to a skin cell line culture.

15. A method according to claim 13 or claim 14 wherein the Gibberellins are Gibberellin A_3.

16. A method according to claim 13 or claim 14 wherein the Gibberellins are a mixture of Gibberellin A_3 and Gibberellin A_7.

17. Compounds of formula (1)

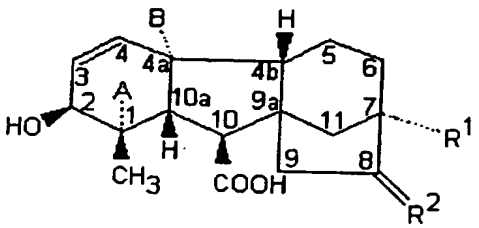


(1)

wherein A is COOR, where R is hydrogen, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, amidine, NR^4R^5 or an unsaturated or saturated ring containing one or more hetero-atoms. R^4 and R^5 may or may not be the same, are hydrogen, or C_{1-20} alkyl, allyl, aryl, arylalkyl or an unsaturated or saturated ring containing one or more hetero-atoms,
B is hydrogen, hydroxyl, mercaptan, halogen,
or A and B together form a -CO-O- linkage,
R^1 is hydrogen, hydroxyl, mercaptan, halogen, amino, azido, NR^4R^5, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, and
R^2 is methylene, hetero-atoms when used in the manufacture of a medicament for the treatment of lesions, wounds, ulcers or related conditions.

18. A method of manufacturing a medicament including combining a compound of formula (1)

15



(1)

Wherein A is COOR, where R is hydrogen, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, amidine, NR^4R^5 or an unsaturated or saturated ring containing one or more hetero-atoms. R^4 and R^5 may or may not be the same, are hydrogen, or C_{1-20} alkyl, allyl, aryl, arylalkyl or an unsaturated or saturated ring containing one or more hetero-atoms,

B is hydrogen, hydroxyl, mercaptan, halogen,

or A and B together form a -CO-O- linkage,

R^1 is hydrogen, hydroxyl, mercaptan, halogen, amino, azido, NR^4R^5, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, and

R^2 is methylene, hetero-atoms with a pharmaceutically acceptable carrier.

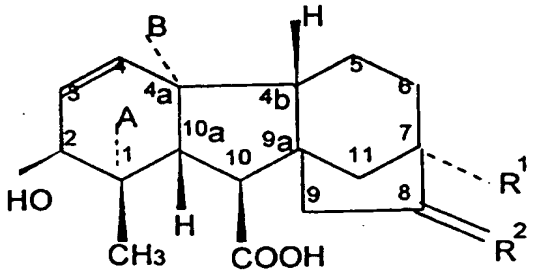
19. A method of treating a wound, lesion or ulcer substantially as hereinbefore described with reference to any one of the Examples.

20. A pharmaceutical composition substantially as hereinbefore described with reference to any one of the Examples.

AMENDED CLAIMS

[received by the International Bureau on 6 May 1996 (06.05.96); original claims 1-20 replaced by amended claims 1-19 (6 pages)]

1. Compounds of formula (1), (Gibberellins), and their pharmaceutically acceptable derivatives when used as promoters of lesion-healing ulcer-healing, wound-healing or cultivation of skin cell lines on animals, including humans, or hair growth on animals not including humans,



(1)

wherein A is COOR, where R is hydrogen, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, amidine, NR^4R^5 or an unsaturated or saturated ring containing one or more hetero-atoms. R^4 and R^5 may or may not be the same, are hydrogen, or C_{1-20} alkyl, allyl, aryl, arylalkyl or an unsaturated or saturated ring containing one or more hetero-atoms,

B is hydrogen, hydroxyl, mercaptan, halogen,

or A and B together form a -CO-O- linkage,

R^1 is hydrogen, hydroxyl, mercaptan, halogen, amino, azido, NR^4R^5, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, and

R^2 is methylene, hetero-atoms.

2. Compounds of claim 1, wherein the Gibberellins are Gibberallin A_3 so that A-B is -CO-O-, R^1 is hydroxyl and R^2 is methylene.

3. Compounds of claim 1, wherein the Gibberellins are a mixture of Gibberellin A_3 and Gibberellin A_7.

4. Compounds of claim 1 wherein the pharmaceutically acceptable derivatives are salts, including alkali metal salts, alkaline earth metal salts, and salts of ammonium, organic bases such as $NR^6R^7R^8R^9$ (where R^6, R^7, R^8, R^9 which may

be the same or not the same, are C_{1-20} alkyl or alkanol, aryl), procaine, or lidocaine.

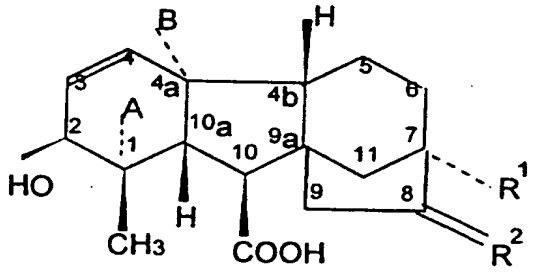
5. The compounds of any one of claims 1 to 4, when used as active therapeutic agents in the treatment of lesions, ulcers, and surface-wounds, surgical wounds, open fractures, bronchitis, dermatitis or thrombophlebitis on a patient in need thereof.

6. The compounds of any one of claims 1 to 4, when used as active therapeutic in the treatment of leg ulcer, peptic ulcer, aphthous ulcer or decubitus, on a patient in need thereof.

7. The compounds of any one of claims 1 to 4 when used as active agents in the promotion of cultivation of skin cell lines for plastic surgery.

8. The compounds of any one of claims 1 to 4 when used as promoters of hair-growth in stimulation of wool production in the farming industry.

9. A pharmaceutical composition including a compound of formula (1)



(1)

wherein A is COOR, where R is hydrogen, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, amidine, NR^4R^5 or an unsaturated or saturated ring containing one or more hetero-atoms. R^4 and R^5 which may or may not be the same, are hydrogen, or C_{1-20} alkyl, allyl, aryl, arylalkyl or an unsaturated or saturated ring containing one or more hetero-atoms,

B is hydrogen, hydroxyl, mercaptan, halogen,

or A and B together form a -CO-O- linkage,

R^1 is hydrogen, hydroxyl, mercaptan, halogen, amino, azido, NR^4R^5, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, and

R^2 is methylene, hetero-atoms;

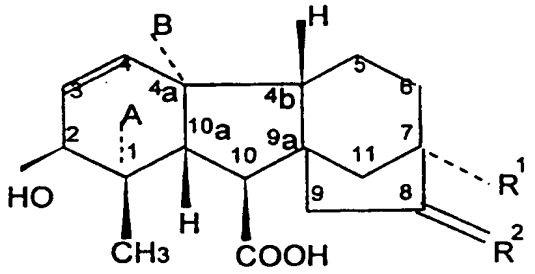
optionally a further active ingredient selected from urea, antibiotics, antiseptic agents, vitamins, β-1,3-glucan, medicinal herbs or mixtures thereof

and a pharmaceutically acceptable carrier.

10. A pharmaceutical composition according to claim 9 wherein the carrier is selected from sucrose, acacia, tragicanth, gelatin, glycerin, cocoa butter, propylene glycol, polyethylene glycols, benzolkamium chloride, polysorbates, buffers, isotonicity-adjusting agents, absorption enhancers, viscosity enhancers, suspending agents, surfactants, lactose, starch or starch derivatives and mixtures thereof.

11. A pharmaceutical composition according to claim 9 or claim 10 containing one or more active ingredients in addition to compounds of formula (I) wherein the additional active ingredient is selected from urea, antibiotics, antiseptic agents, vitamins, β-1,3- glucan, medicinal herbs or mixtures thereof.

12. A method of promoting ulcer-healing or wound-healing including administering an effective amount of a compound of formula (1)

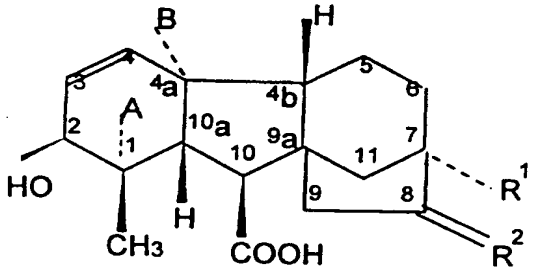


(1)

wherein A is COOR, where R is hydrogen, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, amidine, NR^4R^5 or an unsaturated or saturated ring containing one or more hetero-atoms. R^4 and R^5 may or may not be the same, are hydrogen, or C_{1-20} alkyl, allyl, aryl, arylalkyl or an unsaturated or saturated

ring containing one or more hetero-atoms,
B is hydrogen, hydroxyl, mercaptan, halogen,
or A and B together form a -CO-O- linkage,
R^1 is hydrogen, hydroxyl, mercaptan, halogen, amino, azido, NR^4R^5, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, and
R^2 is methylene, hetero-atoms to a patient in need thereof.

13. A method of promoting cultivation of skin cell lines including providing an effective amount of a compound of formula (1)



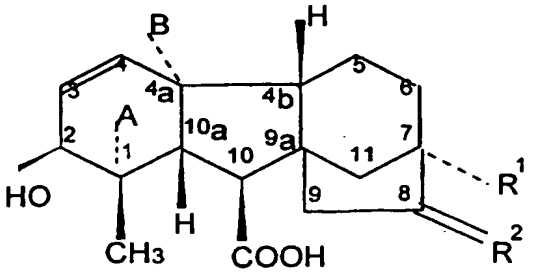
(1)

wherein A is COOR, where R is hydrogen, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, amidine, NR^4R^5 or an unsaturated or saturated ring containing one or more hetero-atoms. R^4 and R^5 may or may not be the same, are hydrogen, or C_{1-20} alkyl, allyl, aryl, arylalkyl or an unsaturated or saturated ring containing one or more hetero-atoms,
B is hydrogen, hydroxyl, mercaptan, halogen,
or A and B together form a -CO-O- linkage,
R^1 is hydrogen, hydroxyl, mercaptan, halogen, amino, azido, NR^4R^5, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, and
R^2 is methylene, hetero-atoms to a skin cell line culture.

14. A method according to claim 12 or claim 13 wherein the Gibberellins are Gibberellin A_3.

15. A method according to claim 12 or claim 13 wherein the Gibberellins are a mixture of Gibberellin A_3 and Gibberellin A_7.

16. Compounds of formula (1)



(1)

wherein A is COOR, where R is hydrogen, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, amidine, NR^4R^5 or an unsaturated or saturated ring containing one or more hetero-atoms. R^4 and R^5 may or may not be the same, are hydrogen, or C_{1-20} alkyl, allyl, aryl, arylalkyl or an unsaturated or saturated ring containing one or more hetero-atoms,

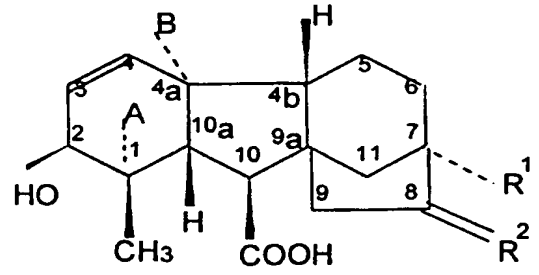
B is hydrogen, hydroxyl, mercaptan, halogen,

or A and B together form a -CO-O- linkage,

R^1 is hydrogen, hydroxyl, mercaptan, halogen, amino, azido, NR^4R^5, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, and

R^2 is methylene, hetero-atoms when used as the active ingredient in the manufacture of a medicament for the treatment of lesions, wounds, ulcers or related conditions.

17. A method of manufacturing a medicament including combining a compound of formula (1)



(1)

wherein A is COOR, where R is hydrogen, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, amidine, NR^4R^5 or an unsaturated or saturated ring containing one or more hetero-atoms. R^4 and R^5 may or may not be the same,

are hydrogen, or C_{1-20} alkyl, allyl, aryl, arylalkyl or an unsaturated or saturated ring containing one or more hetero-atoms,

B is hydrogen, hydroxyl, mercaptan, halogen,

or A and B together form a -CO-O- linkage,

R^1 is hydrogen, hydroxyl, mercaptan, halogen, amino, azido, NR^4R^5, unsubstituted or substituted C_{1-20} alkyl, allyl, aryl, arylalkyl, and

R^2 is methylene, hetero-atoms;

optionally a further active ingredient selected from urea, antibiotics, antiseptic agents, vitamins, β-1,3-glucan, medicinal herbs or mixtures thereof, with a pharmaceutically acceptable carrier.

18. A method of treating a wound, lesion or ulcer substantially as hereinbefore described with reference to any one of the Examples.

19. A pharmaceutical composition substantially as hereinbefore described with reference to any one of the Examples.

1/4

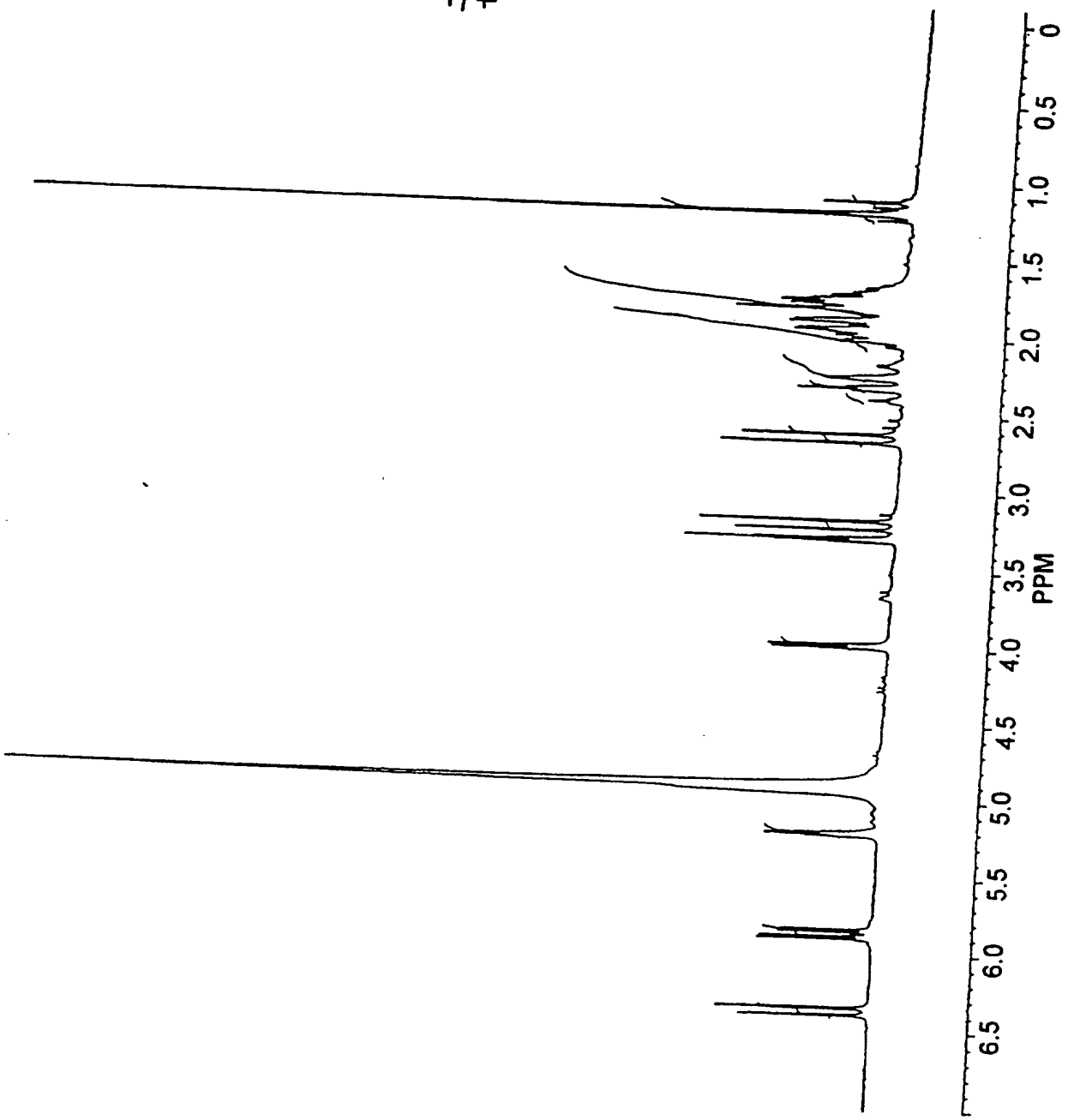


FIG 1

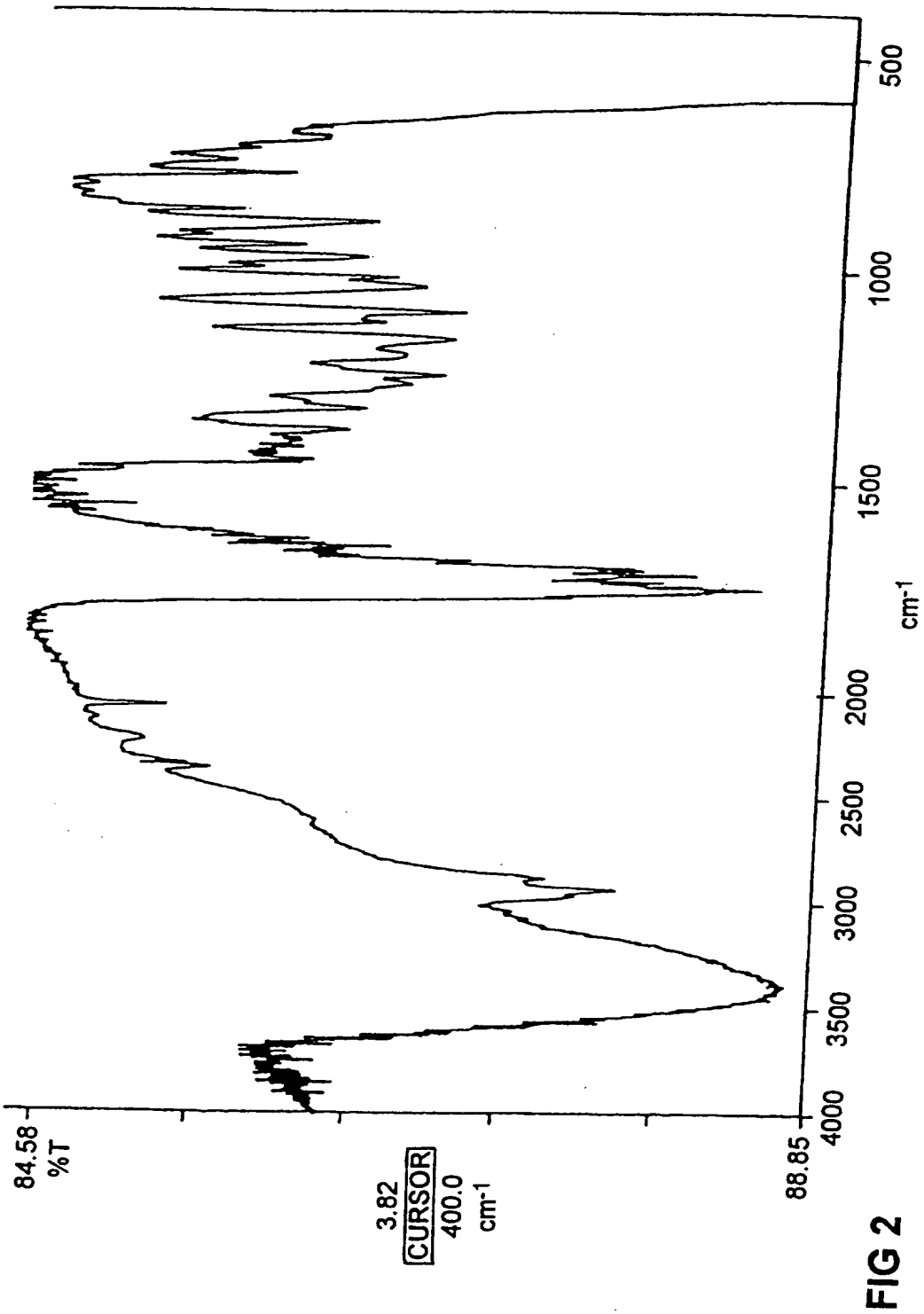

84.58
%T
3.82
CURSOR
400.0
cm-1
88.85
4000
3500
3000
2500
2000
1500
1000
500
cm-1

FIG 2

3/4

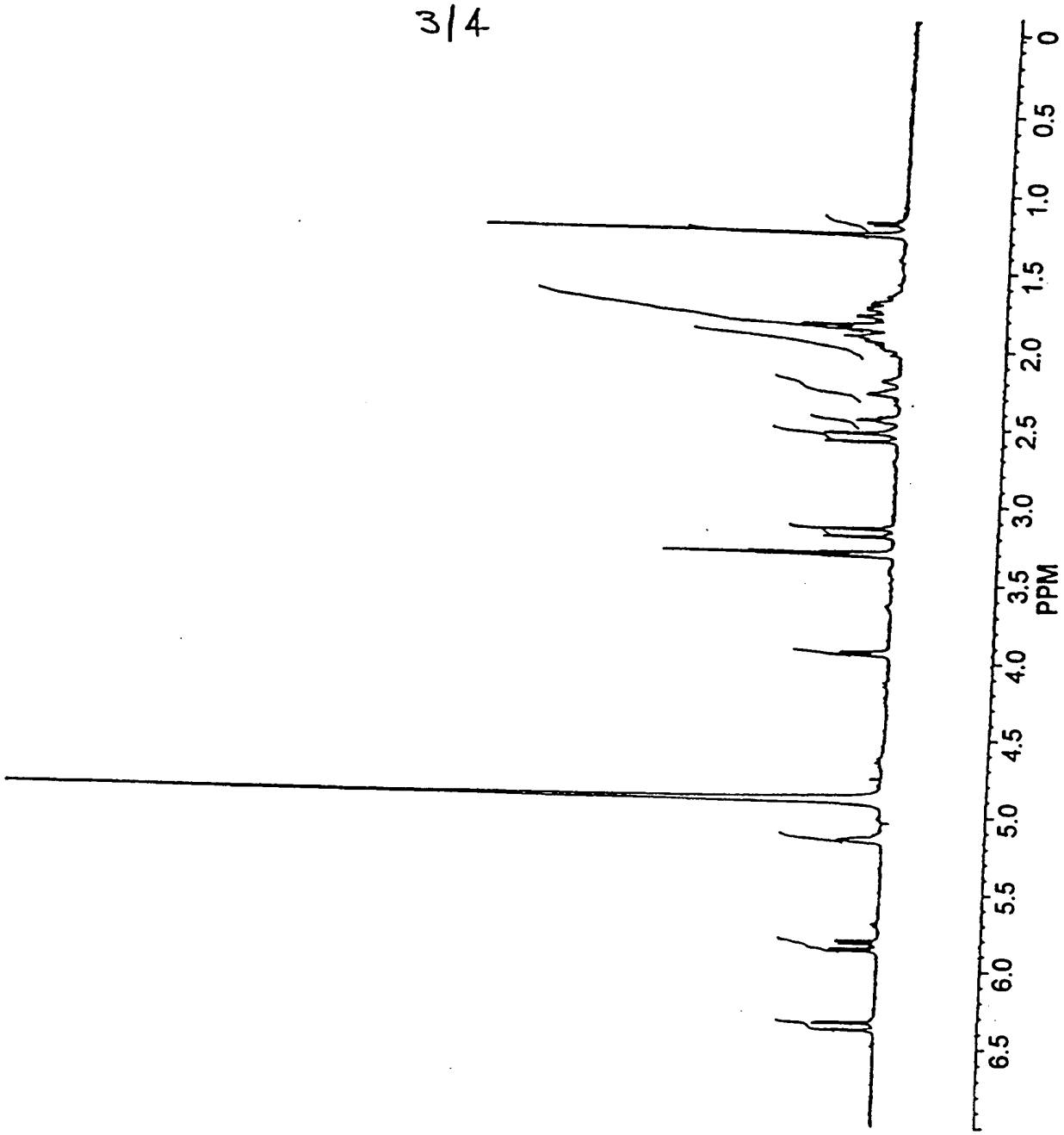


FIG 3

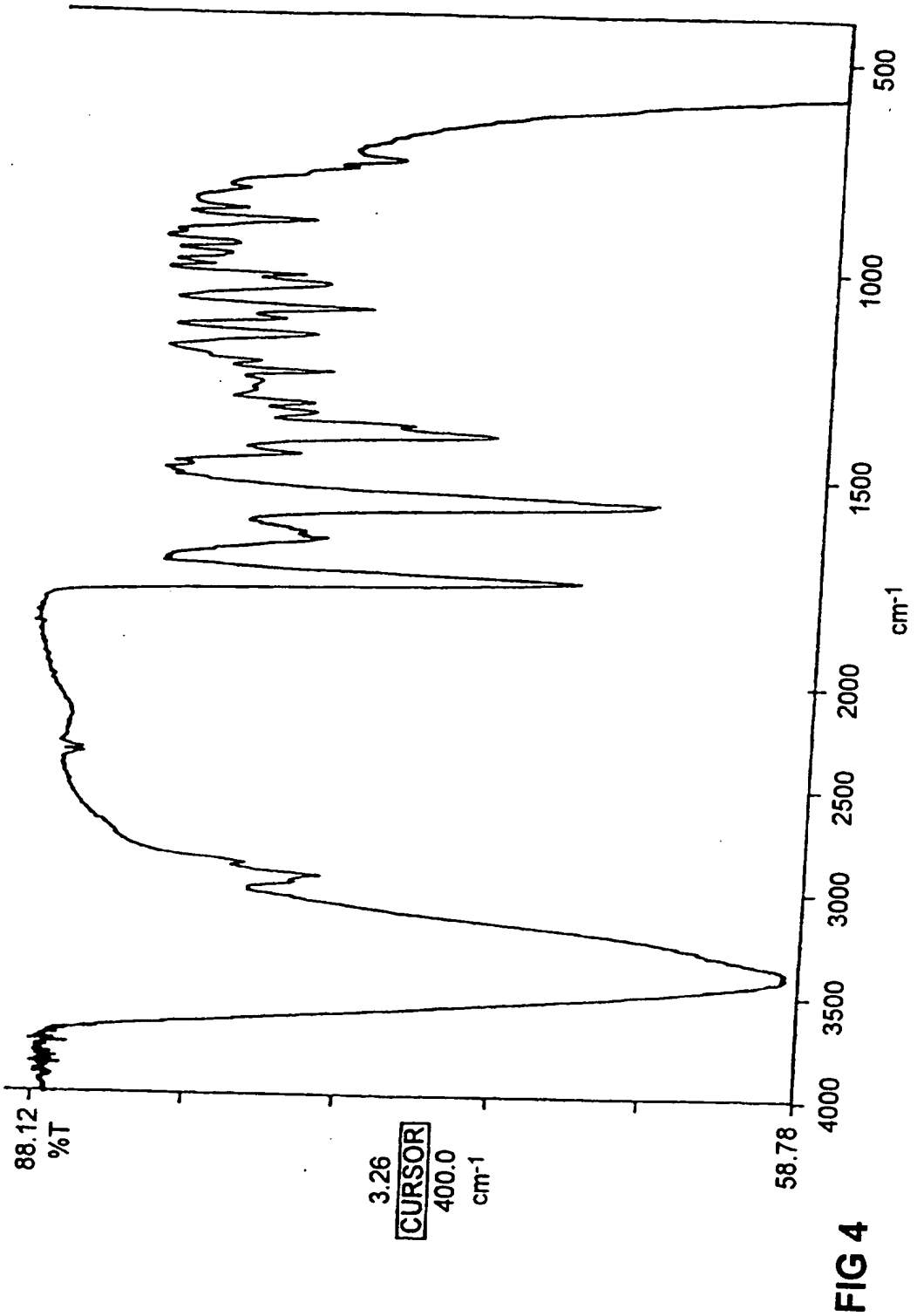

88.12
%T
3.26
CURSOR
400.0
cm-1
58.78
4000
3500
3000
2500
2000
1500
1000
500
cm-1

FIG 4

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 96/00003

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61K 31/365, 31/19, 31/215, 7/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC : A61K 31/365, 31/19, 31/215, 7/06

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU : IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DERWENT)
) A61K and Gibberell:
JAPIO)
CASM (Gibberell:) and (Drug: or Medic: or Pharmaceut:)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AU,B, 23399/84 (595729) (REDKEN LABORATORIES, INC.) 10 May 1984 see whole document	1-4, 9-11, 14, 15, 17, 18, 20
X	AU,A, 66627/94 (ODEN, Per Christer) 24 November 1994 see whole document	1-4, 8-18, 20

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
8 February 1996

Date of mailing of the international search report
12.02.96

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 96/00003

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A, 282951 (NIPPON OIL & FATS CO. LTD.) 21 September 1988 see page 3 line 31	9
X	EP,A, 79074 (KAKUDAI SHOSAN KABUSHIKI KAISHA) 18 May 1983 see whole document	1-4, 8-13, 15-18, 20
X	US,A, 4424232 (RICHARD W. PARKINSON) 3 January 1984 see whole document	1, 2, 4-6, 9-11, 13, 15, 17-20
	FR,A, 259733 (BOUNAN Michael) 23 October 1987 see whole document	

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 96/00003

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
AU	23399/84	DE NO	3245/84 842674	EP WO	126138 8401710	JP US	59501986 4518614
AU	WO 9426240						
EP	282951	DE JP	3886965 63226358	DK	1374/88	US	5081111
EP	79074	CA	1187416	JP	58079913	US	4508708
US	4424232						
FR	259733						

END OF ANNEX